Thyroid Neoplasia as a Late Effect of Acute Exposure to Radioiodines in Fallout*

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This report concerns the recent development of thyroid neoplasia in 82 Marshallese people of Rongelap island who were accidentally exposed to radioactive fallout in 1954 during the testing of thermonuclear devices in the Pacific proving grounds. During the two days before evacuation 64 people on Rongelap island received a whole body gamma dose of about 175 rads and 18 other Rongelap people on a nearby island about 69 rads. In addition they sustained serious skin exposure and significant internal absorption of radionuclides. A third population on the island of Utirik, 150 miles east of Rongelap, received only a slight exposure and this group will only be referred to briefly in this report. By 1957 the radioactive contamination of Rongelap island had reduced sufficiently to allow the people to be returned. At that time a new village was constructed for them (Fig. 1). Fortunately over 200 Rongelap people (relatives of the exposed group) who had not been exposed to fallout returned also and have served as an excellent comparison population.

Annual medical examinations during the past 15 years have documented the acute and late effects of this exposure on these populations[1-3]. The people of Rongelap had early acute signs of exposure including anorexia, nausea and vomiting followed later by the development of significant but transient depression of the formed elements in their blood. However, no infections or bleeding tendencies were noted and no deaths occurred which could be attributed to radiation exposure. No prophylactic or specific therapy was given. Radioactive contamination of the skin resulted

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in the development of lesions ("beta burns") and spotty epilation of the head in the majority of the people between 2 and 4 weeks following exposure. The skin lesions healed within several weeks and the hair regrew by 6 months. Some of the people had slight residual atrophy, scarring and pigment changes of the skin. The acute effects appeared to be more severe in the children than in adults. No acute effects of the internal exposure to the radionuclides were noted in the people and the full significance of this exposure was not appreciated at that time.

Until the development of thyroid abnormalities 5 years ago, only a few possible late effects of exposure were observed in the Rongelap people. These have been described in detail in other reports[1-3] and are only briefly summarized here. During this period the general health of the exposed population remained about as good as that of the unexposed population living on the same island with no illnesses that could be attributed to radiation exposure. A slightly higher death rate was noted in the exposed group but this may have been due to the larger number of older people in that group. Of possible significance has been the continuing slight depression of the mean peripheral blood levels in the exposed population compared with those that were unexposed. About twice the incidence of miscarriages and stillbirths were noted in the exposed women during the first 5 year period but general fertility in the exposed people appears to have been about the same as that in the unexposed based on the number of live births. No malignant lesions of the skin and no cases of leukemia have developed. Two cases of cancer of the female genital tract in exposed women

compared to none in the unexposed group have occurred. Attempts to quantify aging changes did not indicate any premature aging effects in this exposed population. Studies of chromosomes and peripheral blood cultures of the Rongelap people at 10 years post exposure indicated that small numbers of chromosome aberrations of the type usually associated with radiation exposure were still present.

One of the more important findings noted within a few years after radiation exposure was slight retardation of growth in some of the exposed children as evidenced by extensive anthropometric measurements and skeletal maturation studies. The retardation of growth was most notable in boys who had been exposed when less than 5 years of age, particularly in two boys exposed between 15 and 18 months of age[3].

Thyroid lesions.

Estimations of radiation dose to the thyroid gland. Unfortunately the calculations of dose to the thyroid from the absorption of radionuclides in the fallout had to be based on radiochemical urine analyses that were obtained several weeks after the accident. It was known that there were several isotopes of iodine in abundance in the fallout(^{131,132,133,135}I). These iodine isotopes gained entry into the body from inhalation and from consumption of contaminated food and water during the two days before the people could be evacuated from the island. It was calculated that the thyroid gland on the average accumulated roughly 11.2 mCi of ^{131}I on the first day of exposure. The extrapolated dose to the adult thyroid of the people on Rongelap was 160 rads from all the radioiodines plus 175 rads from gamma radiation. Due however, to the smaller size of the thyroid gland in

children and to other factors it was estimated that the thyroid of a 3 to 4 year old child received 700-1400 rads from radioiodines in addition to 175 rads of gamma radiation. In view of thyroid atrophy that developed in 2 boys it must be conceded that the doses to the thyroid in these 2 cases must have been considerably higher.

Early thyroid studies.

Even before the development of thyroid nodules was noted the evaluation of thyroid status of the exposed individuals received considerable attention since it was recognized that the slight growth retardation noted in some of the children might be related to radiation effects on that gland. However, based on physical examinations and serum PBI and cholesterol determinations each individual examined was believed to be euthyroid. Later, studies of serum iodines indicated that the Marshallese normally possess higher levels of iodoproteins than is usually found in other populations. Thus the higher than expected PBI values in some cases may have obscured incipient thyroid deficiency at the time of early observations[4].

Development of thyroid lesions.

Nine years after the accident an asymptomatic thyroid nodule was detected during routine annual physical examinations in a 12 year old girl and the following year two 13 year old girls who had been exposed were also found to have nodules of the gland. Since then increasing numbers of thyroid abnormalities have appeared in the exposed Rongelap people. In 19 people nodularity of the gland has been the prominent finding while in 2 additional boys atrophy of the gland has developed.

The nodules were usually multiple, non-tender and varied in consistency. In some instances enlargement of one or both lobes was noted. Surgical exploration, to be described below, has been carried out in 18 of the 19 nodular thyroid glands. Benign adenomatous lesions were found in all with the presence of malignant lesions also present in 3 of these cases. One adult with somewhat less significant nodularity of the thyroid is still under observation. In view of the seriousness of these developments in the thyroid a panel of experts advised that the people be given supplemental thyroid hormone. This treatment was instituted in September 1965.

Table 1 outlines the incidence of benign nodules (including atrophy of the gland), the malignant lesions and the estimated dose of radiation to the thyroid glands in the various populations under study. The highest incidence of thyroid lesions (89.5%) has been noted in the heavily exposed Rongelap children who were less than 10 years of age at the time of the accident. The absence of lesions in children of the same age in the lesser exposed and unexposed groups is most notable. The incidence of thyroid lesions in the adults of the more heavily exposed group is considerably lower than in the children but is significantly higher than is generally seen in the adult population of the lesser or unexposed groups. (Only one individual has been found to have an adenomatous thyroid lesion in the lesser exposed Rongelap group.)

The first case of carcinoma of the thyroid was discovered in 1965 in a 40 year old woman in the heavily exposed group, 11 years after exposure. At that time the relationship of radiation exposure to the appearance of this lesion was seriously questioned, although such lesions are rare

in the Marshallese. However, in September 1969 surgical exploration of the thyroid on 5 Marshallese with palpable nodules revealed malignant lesions in 3 additional people. Two of the malignant lesions occurred in women in the more heavily exposed Rongelap group, one in a 36 year old female who was 21 years of age at the time of exposure and one in a 22 year old female who was 7 years of age at the time of exposure. This latter case represents the first malignant thyroid lesion to be noted in the group of heavily exposed children who have the highest incidence of benign lesions. These recent findings greatly increase the concern about radiation induced neoplasms in this population. The third individual with a malignant lesion was noted in a woman from Utirik island. Since the dose of radiation received by that group was very low, it is highly improbable that this lesion is attributable to radiation exposure.

Surgical exploration of thyroid nodules.

Thyroid operations have been performed at the following times: 3 in 1964*, 3 in 1965**, 5 in 1966**, 3 in 1968**, and 5 in 1969***.

At surgery the gross appearance of most of the thyroids were lobulated but in addition contained grossly discrete masses (See Figs.2-4). The benign thyroid lesions exhibited multiple nodules varying in size from a few millimeters to several centimeters. They varied from soft to firm in consistency, and were hemorrhagic or in many instances cystic. It was noted in some that there was increased fine vacularity over the surface of the gland similar to that which has been noted in thyroids which had been treated with large doses of ^{131}I for hyperthyroidism. Some of the

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recent patients had received small tracer doses of radioiodine the day before surgery so that the nodular tissue could be measured for radioactive content at the time of surgery. The discrete lesions in many instances showed ^{131}I uptakes which were different from the extra nodular tissue. Most of the discrete benign lesions showed less uptake than the extra nodular surrounding tissue (Fig. 5). Measurement of radioiodine in the malignant tissue was found to be nil compared with the surrounding more normal tissue.

Microscopic examination of the benign lesions revealed marked variation in size of follicles. The cells of some follicles appeared atrophic, while others were hyperplastic, which was reminiscent of iodine deficiency goiter (Fig. 6). In addition to the gross adenomatous masses in the 15 thyroids which were classified as benign there were multiple microscopic clusters of what appeared to be atypical proliferating cells here and there in the parenchyma of some of these thyroids (See Figs.7 and 8).

Microscopically the thyroid carcinomas were considered of low grade malignancy and varied in structure from papillary to mixed papillary and follicular type. Benign adenomatous changes were also noted in the glands. All showed capsular invasion and in 2 cases localized metastases to lymph nodes was present and in 2 other cases blood vessel metastases were noted (Figs. 9 and 10). Total thyroidectomies were performed in all 3 cases of malignancy and a left radical cervical lymph node dissection was carried out in 1 case because spread to lymph nodes was seen. No metastases have been recognized beyond the cervical region in any patients.

Thyroid functions; correlation with retardation of growth in children.

In some children with thyroid lesions, deficiency in serum thyroxine has been correlated with retardation of growth. The most striking instances of hypothyroidism were in two boys who showed marked retardation of statural growth and bone age. By 1964, they had developed obvious atrophy of the thyroid gland with almost complete loss of thyroid function as evidenced by a failure of the thyroid to take up much if any iodine even after TSH stimulation. By this time there were low thyroxine and very high TSH levels in the blood. They showed bony dysgenesis, sluggish Archilles tendon reflexes, puffy faces, and dry skin. Their response to thyroid hormone supplement as evidenced by growth spurt, improved appearance, etc. has been dramatic (See Figs. 11 and 12). Several other children who displayed thyroid nodulariy and whose statural growth was below average showed low or low-normal serum thyroxine values and poor radioiodine uptake after TSH stimulation indicating that their thyroids were functionally impaired and operating near their maximum capacity. Functional deficiency of the thyroid was not demonstrated in adults with nodules or carcinoma of the thyroid.

Influence of physiological stress on thyroid abnormalities.

An assessment was made of the relationship of the development of puberty to the occurrence of thyroid nodules. Degrees of pubescent changes have been recorded annually by a grading system. The two boys that showed greatest retardation of growth had developed atrophy of the thyroid gland before puberty. Here changes associated with puberty were delayed. There may be some association between the apparent increased demand for thyroid

hormone at puberty and the appearance of thyroid nodules since in 10 children thyroid nodules appeared near the expected or actual time of puberty. In 5 other children (2 males and 3 females) in this group the nodules appeared 1 to 3 years after puberty and in the females were associated with pregnancies. In evaluating the influence of puberty and pregnancy it should be pointed out that the latent period between exposure and the development of thyroid abnormalities was fairly constant in all of these children, varying between 10 and 13 years, so that the above findings may have been fortuitous. In the 4 women who developed carcinoma of the thyroid the possible influence of the stress of pregnancy must be considered since all had multiple pregnancies in the years preceding the development of lesions.

Sex incidence.

The ratio of benign thyroid lesions occurring in the Rongelap population was females 1.3 to males 1.0. The findings may be misleading since all of the females in the group exposed at less than 10 years of age had lesions whereas 2 males in the group did not. The fact that all 3 malignant lesions of the thyroid were in females is consistent with reported statistics showing preponderance of such lesions in females[5].

DISCUSSION

At the time of appearance of the first malignant thyroid lesion in the more heavily exposed Rongelap group several years ago numerous benign adenomatous thyroid nodules had appeared which were suspected of being related to the radiation exposure. However such an etiological relationship to the single isolated malignant lesion found at that time was speculative. With the findings of 2 additional individuals with thyroid carcinoma in

this group (3 among 21 thyroid lesions in 67 Rongelap people exposed) makes the etiological role of radiation exposure increasingly probably. For the time being the single malignant lesion found in the thyroid of the woman from Utirik atoll cannot be attributed to radiation exposure because of the low dose of radiation received by the people from that atoll.

The significance of radiation exposure of the thyroid glands in the Rongelap people had not been fully appreciated until the actual appearance of thyroid lesions. More careful review of the dose calculations indicated that considerable exposures from radioactive iodine absorption had probably occurred particularly in the children. The exposure of the Rongelap people was not comparable to exposure of populations from fallout from reactor accidents where radionuclides are chiefly absorbed from contaminated milk obtained from cattle grazing on contaminated pastures. In the Marshall islands there are no cattle and no local milk supply. (Mothers milk may have contributed to the radioiodine absorption in 2 children who were reported to have been nursing at the time of the accident). But there was heavy contamination of food and water supplies on Rongelap and a relative abundance of radioiodines in the fallout. The dose to the thyroid glands was greater by a factor of 2 in adults and a factor of about 7 in children over that to other organs of the body.

Numerous animal studies have demonstrated the role of radiation in the etiology of thyroid neoplasms[6-8]. In the human being the development of thyroid nodules and cancer from X-irradiation[9-10], particularly when the radiation of the gland occurs in infancy and childhood[11-13] is well documented. Development of such lesions from radioiodines has also been

seen in animals but has been less frequently observed in human beings. Eight cases of nodular goiter have been reported by Sheline et al.[9] in their followup study of 250 cases treated for hyperthyroidism. Six of these cases were irradiated before 20 years of age and 4 before 10 years of age. One case showed a possible invasion of the thyroid capsule.

The incidence of thyroid nodularity in the exposed Marshallese is considerably higher than has been reported by Pincus[11] and Hempelmann[13] in their studies of populations who had been exposed to therapeutic X-irradiation of the neck region at a young age. However when comparison is made on a risk per rad basis the incidence is quite comparable with 51 cases per 10^6 persons per rad per year for the Marshallese and 24 cases for 1 group and 64 for a second group 10^6 persons per rad per year calculated by Pincus and Hempelmann. This comparison seems to indicate similar effectiveness per rad of X-radiation compared with per rad dose from radioiodine exposure.

The 3 malignant lesions of the thyroid reported here in the heavily exposed Rongelap people appear to be the first such cases clearly associated with radioiodine exposure with the exception of the one possible malignant thyroid lesion reported by Sheline et al.[9]

Based on the incidence reported by the Trust Territory of carcinoma of the thyroid among the 17,000 Marshallese, the expected incidence in the Rongelap high exposure group would be 0.056 cases over the 15 year period. The finding of 3 cases (5.6% incidence) thus represents a considerable increase over the expected number of cases ($P>0.01$, X^2 test). Among the 157 Utirik people about 0.14 cases would be expected with 1 case reported.

It seems less likely that this single isolated case among the Utirik people would involve radiation etiology in view of the low dose received by this group and the fact that no nodular lesions had been noted among the children. Based on the present incidence of thyroid malignancy in the high exposure Rongelap group the risk for development of this malignancy per 10^6 per person per rad per year is 3 cases for the children exposed at less than 10 years of age, 10 cases for the older people and 5.6 cases for the group as a whole. The risk in the Marshallese children is not inconsistent with that reported by others[13].

It has been generally believed that radioiodine exposure was less effective than X-radiation in producing thyroid lesions based primarily on the fact that few thyroid tumors had been noted following radioiodine therapy[5]. It seems likely, however, that the scarcity of such findings is related to the high doses of radiation used (5-10,000 rads or more in the treatment of hyperthyroidism and 50,000 rads or more for ablation of the gland to ameliorate symptoms in certain diseases). Such doses probably are so destructive that they preclude proliferative activity and malignant transformation in such damaged glands. The increasing incidence of hypothyroidism without tumor formation, years after treatment of hyperthyroid patients with radioiodines illustrates this point. It has been shown that tumor formation in animals is not always a dose dependent phenomenon[15]. Shellabarger et al.[16] showed that breast tumors in rats reached a maximum incidence at about 400 rad and the occurrence of neoplasms fell off with higher doses. Lindsey et al.[8] reported that doses of ^{131}I in rats in excess of 200-400 μCi were less carcinogenic than lower doses.

Mark and Bustad report similar findings in sheep[17]. Though the dose to the thyroid gland in the Marshallese was generally considerably below the dose of ^{131}I used for therapy of hypothyroidism it is likely that the doses received by some of these children were in excess of the optimum carcinogenic range and therefore the true risk per effective rad may be greater in this group. The paradoxical finding of greater risk in the older group appears to be in line with this reasoning. The two stunted Marshallese boys who showed almost complete atrophy of their thyroid glands with no evidence of nodular development are probably comparable to those cases of hypothyroidism developing in patients years after receiving radioiodine therapy. It should be pointed out that the thyroid exposures in the Rongelapese were slightly different from patients treated with ^{131}I because their thyroids were not hyperplastic when exposed and at least part of the radioiodine isotopes to which they were exposed were of shorter half life than ^{131}I. In addition their exposure was complicated by gamma radiation.

There were some factors secondary to radiation exposure that might have enhanced the development of thyroid lesions in the Marshallese. Iodine deficiency or presence of goitrogens in the diet did not appear to be among these. However the physiological stresses of puberty and pregnancy may have played a role in the development of the lesions. For instance the development of 10 cases of nodular goiter in the children during or near the time of puberty might indicate that this stress may have enhanced nodular development. In 3 females that developed thyroid nodules later the demand of multiple pregnancies may have been related. However since the latent

period between exposure and nodule discovery varied only between 10 and 13 years it may be argued that development of thyroid nodules was independent of these stresses. On th other hand it is noteworthy chat all of the women who developed malignant thyroid lesions had multiple pregnancies prior to the appearance of such neoplasms.

The development of thyroid nodules in the Marshallese showed only a slight preponderance in favor of the females (1.3 to 1.0). This is similar to the near equal sex ration reported by Toyooka et al.[12] for thyroid nodules developing in persons irradiated over the neck region in infancy. However, in the case of carcinoma of the thyroid the expected female preponderance occurred[5].

The insidious development of growth retardation in some of the Marshallese children before clinical evidence of thyroid abnormality or deficiency was recognized demonstrates the apparent sensitivity of growth and developmental processes to borderline or subclinical thyroid deficiency. All possible steps are being taken so that the children will adhere to the present thyroid treatment schedule so that thye will achieve satisfactory growth and maturation.

Careful medical surveillance of these exposed people including those on Utirik will be essential in future years. The latent period for the development of cancer was 7 years in one case and 14 and 15 years in the other two. The fact that there may be a longer latent period for the induction of malignant change is borne out by a report by Goolden who noted the development of thyroid cancer 40 years after radiation exposure[18]. It may be that we are just reaching the critical period in the post-radiation observations.

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SUMMARY

Among the 67 people of Rongelap island now living (of the original 82) who were accidentally exposed to radi active fallout in 1954, 3 have developed a malignant lesion of the thyroid, 16 have developed benign nodules of the thyroid and 2 have atrophy of the gland with hypothyroidism. These findings indicate the seriousness of the exposure to radioiodines in fallout. The preponderance of thyroid lesions have occurred in persons who were children less than 10 years of age when exposed. Thyroidectomy, partial to complete, has been carried out in the United States on 18 Marshallese persons. The findings are described. Slight retardation of growth in some of the exposed children is correlated with demonstrable deficiency of the thyroid hormone associated with radiation-induced lesions of that gland. Supplemental thyroid hormone treatment seems to be promoting skeletal growth in some of these children. The possible influence of puberty and pregnancy in the development of the thyroid lesions is pointed out. The calculated risk of a malignant lesion of the thyroid in the Marshallese varied between 3 and 10 cases per 10^6 persons per rad per year for the different age groups. Based on these few cases the risk for thyroid cancer from radioiodine exposure does not appear to be very different from that reported in persons following X-radiation of the neck region as children.

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FIGURES NOT AVAILABLE

LEGENDS

Fig. 1. New village at Rongelap constructed for return of people in 1957.

Fig. 2. Exposure of thyroid at surgery showing nodules. The nodules were benign.

Fig. 3. Excised thyroid showing benign nodules.

Fig. 4. Excised thyroid showing malignant nodule in upper right lobe.

Fig. 5. Autoradiograph of section made through a nodule of a thyroid with benign lesions. Lack of grains (superimposed blackening) shows that adenoma in center is nonfunctioning. H. and E. stain, magnification X14.

Fig. 6. Section of thyroid showing 2 benign papillary adenomas. H. and E. stain, magnification X14.

Fig. 7. Multiple clusters of what appear to be atypical proliferating cells in a thyroid which contains several large discrete adenomas. The lesions were considered benign. H. and E. stain, magnification X20.

Fig. 8. An area of atypical proliferating cells in a thyroid which had developed multiple discrete benign adenomas. H. and E. stain, magnification X70.

Fig. 9. Follicular carcinoma of the thyroid showing capsular invastion in a 35 year old woman exposed to fallout. This represented a discrete mass as shown in Fig. 4. There was no lymph node metastasis. H. and E. stain, magnification X26.

Fig. 10. Papillary carcinoma demonstrating extensive connective tissue invasion within the lobe. This patient had multiple cervical lymph node metastasis. H. and E. stain, magnification X64.

FIGURES NOT AVAILABLE

Fig. 11. One of two boys who have developed mxedema. Picture on left at 12 years of age at the beginning of treatment with thyroid hormone; picture on right shows marked growth and improvement in appearance after 3 years of treatment.

Fig. 12. Relative patterns of skeletal maturation and statural growth (connected to developmental ages) in the two boys who had marked hypothyroidism. Comparison is with unexposed boys. Note the dramatic change in slope of growth curves after thyroid hormone administration.

Note to the Editor:

If the Editor wishes he may group together figures 5-8 and figures 9 and 10.

Table I

Thyroid Lesions in Marshallese, March 1969

Island Group (Radiation Dose-Gamma)	Age at Exposure	Estimates Thyroid Dose (Rads, Radioiodines*)	Thyroid Lesions Per Cent**	Malignant Lesions Per Cent**
Rongelap (175 Rads)	<10	500-1400	89.5(17/19)	5.3(1/19)
	>10	160***	8.8(3/34)	5.9(2/34)
	all	-	39.6(21/53)	5.7(3/53)
Rongelap (69 Rads)	<10	275-550	0.0(0/6)	-
	>10	55	12.5(1/8)	-
	all	-	7.1(1/14)	-
Utirik (74 Rads)	<10	55-100	0.0(0/40)	-
	>10	14	5.1(3/59)	1.7(1/59)
	all	-	3.0(3/99)	1.0(1/99)
Rongelap (unexposed)	<10	-	0.0(0/61)	-
	>10	-	2.3(3/133)	-
	all	-	1.5(3/194)	-

*Dose from $^{131,132,133,135}I$.

** Based on number now living.

*** Children 10-20 years of age at exposure received doses between 160 and 500 rads.